Safety and efficacy of fluoxetine on functional outcome after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial

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Effects of fluoxetine on functional recovery after acute stroke (AFFINITY): a randomised, double-blind, placebo-controlled trial.

AFFINITY Trial Collaboration*

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Summary

Background

Trials of fluoxetine for recovery after stroke report conflicting results. The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial aimed to determine if daily fluoxetine for 6 months after stroke improves functional recovery in Australasian and Vietnamese patients.

Methods

AFFINITY was a randomised, parallel-group, double-blind, placebo-controlled trial conducted in 43 hospital stroke units in Australia (n=29), New Zealand (4), and Vietnam (10). Eligible patients were adults with a clinical diagnosis of stroke in the previous 2-15 days and a persisting neurological deficit. Patients were randomised via a web-based system using a minimisation algorithm to once daily, oral fluoxetine 20mg or matching placebo for 6 months. Patients, investigators and outcome assessors were masked to the treatment allocation. The primary outcome was functional recovery, measured by the modified Rankin scale (mRS), at 6 months. The primary analysis was an ordinal logistic regression of the mRS at 6 months, adjusted for minimisation variables. Analyses were according to the patient's treatment allocation. The trial is registered with the ACTRN registry, number 12611000774921.

Findings

1280 patients were recruited in Australia (n=532), New Zealand (n=42) and Vietnam (n=706) between 11 January 2013 and 30 June 2019; 642 were allocated fluoxetine and 638 placebo. Adherence to trial medication (mean 167 [SD 48] days) was similar between groups. At 6 months, mRS data were available in 624 (97.2%) patients allocated fluoxetine and 632 (99.1%) placebo. The distribution of mRS categories at 6 months was similar in the fluoxetine and placebo groups (adjusted common odds ratio 0.936, 95% CI 0.762-1.150; p=0.53), and consistent among all pre-defined subgroups. Compared to placebo, patients allocated fluoxetine had more falls (20 [3.12%] vs 7 [1.10%]; p=0.02), bone fractures (19 [2·96%] vs 6 [0.94%]; p=0.01) and epileptic seizures (10 [1.56%] vs 2 [0.31%]; p=0.04) at 6 months.

Interpretation

Fluoxetine 20mg daily for 6 months after acute stroke did not improve functional recovery and increased the risk of falls, bone fractures, and seizures. These results do not support the use, or further trials, of fluoxetine to improve recovery after stroke.

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RESEARCH IN CONTEXT

Evidence before this trial

We undertook a Cochrane systematic review and searched Cochrane and clinical trial registers; MEDLINE, Embase, PubMed, and other biomedical databases; from their inception to 16 July 2018; for randomised controlled trials (RCTs) that recruited stroke patients who had survived up to one year, and randomised them to a selective serotonin reuptake inhibitor (SSRI), at any dose, for any period, and any indication; or to usual care or placebo. We identified 63 RCTs that compared any SSRI with control in 9168 stroke survivors. About half of the trials required patients to have depression. Potential improvements in disability with fluoxetine were only present in trials at high risk of bias. A meta-analysis of the three trials at low risk of bias (n=3356 patients) found no effect of any SSRI compared to control on functional independence (risk ratio [RR] 1.00, 95% CI 0.91 to 1.09; p = 0.99) or disability score (standardised mean difference [SMD] -0.01, 95% CI -0.09 to 0.06; p = 0.75). The evidence before this trial suggests that SSRIs do not improve functional recovery after stroke, but doubt remains because this meta-analysis was dominated by one large trial, the FOCUS (Fluoxetine Or Control under Supervision) trial (n=3127), in UK patients.

Added value of this trial

The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY) trial externally validates the the FOCUS trial and Cochrane systematic review of RCTs of SSRIs for stroke recovery in an independent population of Australasian and Vietnamese stroke patients, reinforcing the conclusion that fluoxetine does not improve functional recovery after stroke. The AFFINITY trial also adds further data regarding the potential hazards of treating acute stroke patients with fluoxetine 20 mg daily for 6 months, including increased risks of falls, fractures, and seizures.

Implications of all the available evidence

For clinicians, SSRIs should not be prescribed routinely to improve functional recovery after stroke because they are ineffective and increase serious adverse events. For researchers, a pooled analysis of individual patient data from completed RCTs of SSRIs for stroke recovery is needed to examine the effects of SSRIs in specific patient subgroups, such as those with hemiparesis, severe stroke, and cognitive impairment; and on specific outcomes, such as the mRS, motor domains of the Stroke Impact Scale, falls, fractures and seizures. Until these results are available, further trials of fluoxetine for stroke recovery are not recommended.

Introduction

Stroke is the second leading cause of disability-adjusted life years globally.[1,2] Fluoxetine, a selective serotonin re-uptake inhibitor (SSRI), may improve functional recovery and reduce disability after acute stroke. Fluoxetine exerts neuro-protective and neuro-regenerative effects in pre-clinical models of acute brain ischaemia.[3,4] In the FLuoxetine for motor recovery After acute ischaeMic strokE (FLAME) trial, a double-blind, randomised controlled trial (RCT) in 118 patients with acute ischaemic stroke and moderate to severe motor deficits, fluoxetine 20 mg once daily significantly improved motor and functional recovery over 3 months.[5] A subsequent Cochrane systematic review of 52 RCTs of SSRIs for stroke recovery in 4059 patients concluded that SSRIs may improve disability but, given methodological limitations and heterogeneity of the available studies, more definitive, larger trials were required.[6]

Hence, our international collaborative group designed and undertook three clinical trials of fluoxetine in the United Kingdom (Fluoxetine Or Control Under Supervision [FOCUS]), Sweden (Efficacy of Fluoxetine–A Randomised Controlled Trial in Stroke [EFFECTS]) and Australia, New Zealand and Vietnam (Assessment oF FluoxetINe In sTroke recoverY [AFFINITY]).[7,8] The FOCUS trial (n=3127) reported that fluoxetine 20 mg given daily for 6 months after stroke did not improve functional outcomes but reduced the occurrence of depression and increased the frequency of bone fractures.[9] The results were consistent with reports of the effectiveness of fluoxetine as an antidepressant,[10] and of an increased risk of fractures in older people taking SSRIs.[11,12] However, as only two thirds of FOCUS trial patients took the trial medication for at least 150 of the prescribed 180 days, a modest, but important, effect of trial medication on functional outcome may have been missed.[9] Moreover, as 96% of patients in FOCUS were white, the results may not be generalisable outside of the UK.[9] Hence, the AFFINITY and EFFECTS trials continued to recruit patients in parallel until 30 June, 2019.

Herein, we report results of the AFFINITY trial, which aimed to evaluate whether a 6-month course of fluoxetine is safe and effective, compared to placebo, for improving functional recovery after recent stroke in an ethnically diverse population. The results of the EFFECTS trial are reported in a parallel publication.[13]

Methods

Study design and participants

AFFINITY was a randomised, parallel group, double-blind, placebo-controlled clinical trial conducted in 43 hospital stroke units in Australia (n=29), New Zealand (4), and Vietnam (10). The trial protocol (appendix) was approved by the Royal Perth Hospital Ethics Committee on 24 February, 2012 (approval number EC2011/131), and subsequent amendments to the protocol to facilitate trial recruitment were also approved. All participating sites received approval from their ethics committee and institutional review board. The trial protocol[7] and statistical analysis plan[8] were published before recruitment was completed.

Eligible patients were adults (aged ≥18 years) with a clinical diagnosis of acute stroke within the previous 2-15 days, brain imaging consistent with ischaemic or haemorrhagic stroke (including a normal CT brain scan), and a persisting neurological deficit that produced a modified Rankin scale (mRS) score ≥1. Patients were excluded if there was any definite indication for fluoxetine (e.g. depression), or contraindication to fluoxetine (e.g. history of epilepsy, bipolar disorder, drug overdose, allergy to fluoxetine, or any recent medication that could interact with fluoxetine; or biochemical evidence of hepatic impairment [serum alanine aminotransferase (ALT) > 120 U/l], renal impairment [creatinine > 180 µmol/l or estimated glomerular filtration rate (eGFR) < 30ml/min/1.73m^2], or hyponatremia [sodium < 125mmol/L]); if patients were unlikely to be available for follow-up during the subsequent 12 months; if patients had another life-threatening illness that would make 12-month survival unlikely [e.g. terminal malignancy]; if patients were women and pregnant, breast-feeding or of child-bearing age without the use of contraception; or if patients were enrolled in another clinical trial of an investigational medicinal product or device.

Written informed consent was obtained from each patient or, if the patients were unable to provide consent, from their legally approved surrogate.

Randomisation and masking

The patient's clinician entered the patient's baseline data (table 1) into a secure, password-protected, centralised web-based randomisation system which checked the data for completeness and consistency and then generated a unique study identification number and treatment pack number which corresponded to fluoxetine or placebo in a 1:1 ratio. A minimisation algorithm[14] was used to achieve balance between the treatment groups in four predictors of the primary outcome (mRS): time after stroke onset (2-8 vs 9-15 days), presence

of a motor deficit (National Institutes of Health Stroke Scale [NIHSS] questions 5 and 6), presence of aphasia (NIHSS question 9), and probability of survival free of dependency (mRS 0-2) at 6 months (0.00 to ≤0·15 vs >0·15-1.00) as calculated using a previously validated prognostic model comprising six baseline prognostic variables (age, living alone before the stroke, independent in activities of daily living before the stroke, and able to talk, lift both arms off the bed, and walk unassisted at the time of randomisation).[15]

All patients, carers, investigators, and outcome assessors were masked to the allocated treatment by use of placebo capsules that were visually identical to the fluoxetine capsules even when broken open.

Procedures

Fluoxetine 20mg capsules or matching placebo capsules were administered to patients orally, once daily, for 6 months. If the patient was unable to swallow, the capsules could be broken open and the contents administered via an enteral feeding tube.

Siegfried Malta Ltd, Hal Far, Malta, manufactured the capsules containing fluoxetine 20mg according to Good Manufacturing Practice (certificate MT/008HM/2017). Arena Pharmaceuticals GmbH, Zofingen, Switzerland, packed the capsules for Amneal Pharmaceuticals Pty Ltd, South Yarra, Australia, which was the Therapeutic Goods Administration (TGA) licence holder (sponsor) for the finished product in Australia. Pharmaceutical packaging professionals (PPP) Pty Ltd, Port Melbourne, Australia purchased the fluoxetine capsules and manufactured the matching placebo capsules. PPP packaged the trial medication in patient kits, labelled the bottles with trial-specific treatment codes (fluoxetine or placebo), and packaged, stored and distributed the medication. The patient kits in Australian and New Zealand comprised two bottles, each containing 110 capsules, which were dispensed at randomisation and day 90. An extra 20 capsules were a reserve in the event of any delay in attending the day 90 follow-up, or any loss or spillage of capsules. For patients in Vietnam, the kits comprised 6 bottles of trial medication, each containing 35 capsules. One bottle was dispensed at randomisation, two bottles at day 28, and three bottles at day 90. The TGA of the Australian government's Department of Health approved the export of trial medication to New Zealand and Vietnam (approval Ref No: EX17/336513).

All patients received organised, interdisciplinary care and rehabilitation in stroke units.

Patients recruited in Australia and New Zealand were assessed by site investigators at 28 days (1 month) and 90 days (3 months) post-randomisation in the hospital ward or outpatient clinic or via telephone or email; or, failing that, by a study nurse at the patient's residence. Follow-up at 180 days (6 months) was by postal questionnaire or telephone by trained staff in the trial coordinating centre in Perth, Australia. Patients recruited in Vietnam were assessed by the site investigator at 28, 90 and 180 days post-randomisation in the hospital ward or outpatient clinic, or via telephone or email; or, failing that, at the patient's residence. If the patient was unable to complete the assessments, assistance was sought from their proxy (next of kin, close family member or carer). Each assessment recorded the primary outcome (mRS), secondary outcomes (table 2), safety and adverse events (table 3), all current medications, and adherence to trial medication. Serum sodium, eGFR, and liver function were measured at the first (28 day) follow-up visit if clinically appropriate. Adherence to trial medication was assessed by asking: 'On average, since the last follow-up, how many times per week was the trial medication taken? '0, 1-2, 3-4, 5-6 or 7 times per week'; and by pill counts and collection of returned trial bottles. Bottle and pill counts were conducted by hospital trial pharmacists, and entered on a drug accountability form. Any interruption to trial medication was recorded as temporary or permanent, together with the dates and reasons for stopping and re-starting.

If patients developed new depression requiring treatment during the trial treatment period, the protocol recommended continuation of trial medication and consideration of non-pharmacological (e.g. psychological) interventions. If antidepressant medication was considered necessary, referral to a psychiatrist was recommended for consideration of potential interactions of any new medication with fluoxetine and risks of serotonin toxicity.

There were 57 protocol violations in 56 patients (4.4%): 20 (1.6%) patients were prescribed open-label fluoxetine; 8 (0.6%) were prescribed another SSRI; 16 (1.3%) lost their trial medication or did not take the trial medication as prescribed; 4 (0.3%) took medications that could interact with fluoxetine (e.g. antipsychotic, tramadol); 7 (0.5%) patients were more than 14 days late for a scheduled follow-up; one patient enrolled in another trial was deemed

ineligible, and four patients had a final diagnosis other than stroke (table 1). Emergency unblinding was not necessary for any patient.

Outcomes

The primary outcome was functional status, as measured by the mRS, at 6 months after randomization.[16] The mRS is an ordinal scale which assigns patients to seven ordered, but not equally spaced, levels of functional ability, ranging from 0 (symptom free) to 6 (dead).

Secondary outcomes at 6 months were survival, depression (PHQ-9 score $\geq$ 15[17]), cognition (Telephone Interview for Cognitive Status [TICSm][18]), communication, motor function, overall health status (Stroke Impact Scale [SIS] version 3.0[19]), fatigue (vitality subscale of the SF-36[20,21]) and health-related quality of life (HRQoL) using the EQ-5D-5L.[22] A new diagnosis of depression requiring treatment with antidepressants was assessed at 1, 3 and 6 months by asking patients if they had been diagnosed with depression since each of their previous assessments, and verifying the diagnosis and treatment plan with their clinician.

Serious adverse events at any time during follow-up included recurrent stroke (ischaemic or haemorrhagic), acute coronary syndromes, upper gastrointestinal bleeding requiring blood transfusion and/or endoscopy, other major bleeding (subdural, extradural, ocular, lower gastrointestinal) requiring blood transfusion or procedural intervention, falls with injury, new bone fractures, epileptic seizures, symptomatic hypoglycaemia (blood glucose < 3mmol/l), symptomatic hyperglycaemia (blood glucose > 22mmol/l), new hyponatraemia (blood sodium < 125mmol/l), attempted suicide or self-harm, and death.

Statistical analysis

A detailed statistical analysis plan was formulated and published before recruitment was completed and without awareness of any unblinded data.[8]

We estimated from other concurrent studies of patients with acute stroke that 42.2% of patients assigned placebo would be functionally independent (mRS 0-2) at 6 months after randomisation.[23,24] We calculated the odds ratio (OR) of functional independence (mRS 0-2) with fluoxetine vs placebo in the FLAME study[5] to be 3.57 (95%CI: 1.2 to 10.6). We

considered a conservative estimate of the effect of fluoxetine may be toward the lower 95% CI of the OR estimate reported in FLAME (e.g. OR 1.34). If fluoxetine increased the proportion of patients who were functionally independent at 6 months by an OR of 1.34, from 42.2% (placebo) to 49.4% (fluoxetine), this would be clinically important and consistent with our Cochrane review[6] – that is, a 7.2% absolute increase in functional independence in patients allocated fluoxetine compared with placebo. Assuming a common OR of 1.34 for each cut-point across the mRS (e.g. 0 vs 1-6, 0-1 vs 2-6, etc) in the proportional odds logistic model, we estimated that the trial would require 1600 patients to have 90% power, if up to 10% of patients dropped out before final follow-up.[8,25]

All analyses, including primary and secondary outcomes and adverse events, were by intention-to-treat, according to the treatment allocation. A secondary safety analysis was undertaken according to the treatment patients received rather than what they were randomly allocated.

The primary analysis was an ordinal analysis of the mRS scores at 6 months in each treatment group using ordinal logistic regression and after adjusting for the baseline factors included in the minimisation algorithm.[8] The ordinal analysis of mRS was undertaken by treatment allocation, under the assumption of proportional odds in the model. The result was expressed as a common OR (less than 1.0 favoured placebo) and its 95% confidence interval (CI). We also performed 6 binary unadjusted logistic regressions, each corresponding to the 6 possible dichotomisations of scores on the mRS.

Secondary analyses compared the following outcomes at 6 months follow-up in each treatment group: survival, depression (changes in PHQ-9 scores and proportion with PHQ-9 $\geq$ 15),[17] cognition (TICSm scores),[18] communication (SIS),[19] motor function (SIS),[19] overall health status (SIS),[19] HRQoL (EQ-5D-5L),[22] new diagnosis of depression requiring treatment with antidepressants, fatigue (vitality domain of the SF-36)[20,212], trial medication adherence and cessation, and serious adverse events. The frequencies of categorical outcome events, including adverse events, in each treatment group were compared using Fisher's exact test. For continuous outcomes, the mean or median in each group, depending on the distribution, were calculated with measures of dispersion (standard deviation [SD] or inter-quartile range [IQR]). The probability that outcome measures in the treatment group were significantly different from those observed in the placebo group were calculated and expressed as p-values.

Pre-specified subgroup analyses of the effect of fluoxetine vs placebo on the primary outcome were undertaken for key baseline variables, including country of randomisation (Australia/New Zealand vs Vietnam), age (≤70 vs >70 years), time from stroke onset to randomisation (2-8 vs 9-15 days), stroke pathology (ischaemic vs haemorrhagic), stroke severity (NIHSS scores 0-5 vs >5), motor deficit (present vs absent), aphasia (present vs absent), probability of survival free of dependency (0.00 to ≤0.15 vs >0.15 to 1.00), self-reported depression at baseline, and source of informed consent.[8]

We also undertook pre-specified per-protocol analyses, which sequentially excluded subgroups of patients who did not meet our eligibility criteria or had incomplete adherence to the trial medication.

Post-hoc sensitivity analyses of the primary outcome were undertaken to evaluate the possible effect of including those patients who were lost to follow-up. We tested the robustness of the results by assuming two extreme imputation scenarios: one favouring fluoxetine where all patients with a missing mRS were imputed a score of 0 in the fluoxetine arm and a score of 6 in the placebo arm, and another scenario favoring placebo where the imputation was reversed.

Statistical analyses were undertaken with SAS, version 9.4

An independent data monitoring committee (DMC) oversaw the study. The unmasked trial statistician (Q Yi) prepared analyses of the accumulating data, which the DMC reviewed in strict confidence at least once a year.

The trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12611000774921.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 1280 patients consented and were randomised at 43 sites in Australia, New Zealand and Vietnam between 11 January, 2013 and 30 June, 2019. Recruitment was terminated before the target sample size of 1600 patients was reached as grant funding expired on 31 December 2019.

642 patients were randomly allocated to fluoxetine and 638 to placebo. One patient did not meet our eligibility criteria after randomisation because of later discovery of participation in another clinical trial of an investigational medicinal product. In four patients, the initial diagnosis was revised to be non-stroke after review of investigations at the one month follow up (table 1).

Baseline characteristics in the two treatment groups were balanced (table 1)

By 6 months, 22 (1.7%) patients had withdrawn consent for follow-up and a further 2 (0.2%) patients were lost to follow-up (fig 1). There was no difference in the methods of follow-up between treatment groups (appendix table 1, p8). Trial medication was started in 1273 patients, and it was temporarily and permanently stopped in 158 and 208 patients respectively, before the 6-month follow-up (appendix, table 2, p9). There was no significant difference between treatment groups in temporary and permanent discontinuation of trial medication (appendix table 2, p9) or time to permanent discontinuation (p=0.75; appendix figure 1, p14). There were also no significant differences between groups in compliance with trial medication at one (p=0.57), three (p=0.94) or six (p=0.92) months (appendix table 3, p10). The mean duration of trial treatment during the 6 months follow-up was 167 days (SD 48.1) days.

The primary outcome, the mRS at 6 months, was assessed and analysed in 624 (97.2%) patients allocated fluoxetine and 632 (99.1%) placebo. An ordinal comparison of the distribution of patients across the mRS categories at 6 months, adjusted for variables included in the minimisation algorithm, was similar in the two groups (common OR 0.936, 95% CI 0.762-1.150; p=0.53; figure 2). A common OR <1.0 favours placebo. The unadjusted analysis produced similar results (common OR 0.966, 95%CI 0.790-1.181; p=0.74; appendix table 4, p11). The assumption of proportional odds in the model of mRS by treatment was upheld in the score test for proportional odds assumption (p=0.44 unadjusted). Comparison of

dichotomised mRS scores (0–2 vs 3–6) also showed no significant difference between treatment groups (unadjusted OR 0.855, 95%CI 0.670-1.091; p=0.21; post-hoc adjusted OR=0.823, 0.628-1.077; p=0.16; appendix table 4, p11). There was also no difference between groups in other dichotomies of the mRS (appendix table 4, p11).

Analysis of the primary outcome showed no significant interactions or modification of the effect of fluoxetine across several pre-specified subgroups (appendix figure 2, p15).

Secondary efficacy outcome measures at 6 months are shown in table 2. Patients allocated fluoxetine had better mood and emotional control, as measured by higher scores in the SIS domain of mood/emotions compared to placebo (p=0.003), but there were no significant differences between treatment groups in the other 10 domains of the SIS (including measures of motor function [strength, hand ability, mobility] and daily activities), other assessment scales, or death. There was a reduction in new diagnoses of post-stroke depression which was not statistically significant (33 [5.14%] fluoxetine vs 46 [7.21%] placebo; absolute risk difference 2.07%; 95% CI -0.57% to 4.41%]).

Adverse events at 6 months are shown in table 3. Compared to patients allocated placebo, those allocated fluoxetine had more falls causing injury (20 [3.12%] vs 7 [1.10%]; difference 2.02% [95CI: 0.45-3.59]; p=0.02), bone fractures (19 [2·96%] vs 6 [0.94%]; difference 2.02% [0·51–3.53]; p=0·01) and epileptic seizures (10 [1.56%] vs 2 [0.31%]; difference 1.24% [0.19-2.30]; p=0.04). There were no significant differences between treatment groups in other events at, or during, the 6 months follow-up, including survival (p = 0.71, appendix, figure 3, p16). Trial medication was stopped by 68 patients (27 allocated fluoxetine, 41 placebo) due to a suspected adverse reaction to the medication. No patients required a reduction in dose of trial medication (e.g. alternate daily) and there were no treatment-related deaths.

The primary results were not altered by sensitivity analyses confined to patients who adhered to the trial protocol and allocated treatment (appendix table 5, p12).

A post-hoc analysis, which consisted of imputing missing mRS data under two extreme scenarios, also produced consistent, non-significant results for the most extreme scenario in favour of fluoxetine (unadjusted OR 1.082, 95%CI 0.887-1.320; p=0.44; adjusted OR 1.054, 0.861-1.291; p=0.61), and for the most extreme scenario in favour of placebo (unadjusted OR 0.860, 0.705-1.050; p=0.14; adjusted OR 0.833, 0.680-1.020; p=0.09).

Discussion

The main finding of the AFFINITY trial was that adding fluoxetine 20mg daily for 6 months after acute stroke to interdisciplinary stroke unit care did not improve functional outcome at 6 months in an ethnically diverse population. Other major findings were that fluoxetine improved mood and emotional control but increased falls, fractures, and epileptic seizures at 6 months.

Key strengths of the trial are that it was undertaken in stroke units throughout Australia, New Zealand and Vietnam where the AFFINITY trial medication was added to best-practice, comprehensive interdisciplinary stroke care and rehabilitation. Several potential sources of systematic error (bias) in the assessment of fluoxetine vs placebo were minimised. Systematic pre-treatment differences in comparator groups (selection bias) were minimised by concealed, central, web-based randomisation. Adherence to trial medication was high and similar between treatment groups (performance bias). Systematic differences between groups in other care provided (performance bias) and reporting and assessment of outcome events (observer detection bias) were minimised by masking of patients, investigators and adjudicators to the allocated treatment. Follow up for the primary outcome was high and there was no difference between groups in withdrawals from treatment (attrition bias). Random error was reduced to some extent by almost complete follow-up of a large number of patients (n=1256, 98%), which was a higher proportion than planned in our sample size calculations (90% of 1600; n=1440). The inclusion of an international mix of ethnic groups managed in different health care systems, and a comprehensive array of secondary outcome measures, including cognition, mood and motor scales, support the external validity (generalisability) of the trial results.

Potential limitations of the trial include our failure to recruit the target sample size of 1600 patients due to funding constraints (1280 patients recruited; 1256 with primary outcome data vs 1440 planned to have primary outcome data). We also failed to recruit a larger number of patients with severe, disabling stroke. Hence, the proportion of patients assigned placebo who recovered functional independence (mRS 0-2) at 6 months was higher (n=458, 72%) than estimated in our sample size calculations (42%). The dose of fluoxetine was 20 mg once daily because this was the dose reported to be effective in the FLAME trial[5] and used in other fluoxetine trials for stroke recovery,[6] and is less likely to cause adverse effects than higher doses. However, we did not test higher doses of fluoxetine. Our measures of adherence to trial medication by self-report and capsule-counting were prone to error (e.g. the absence of tablets

in the bottles returned to investigators may not necessarily mean adherence to taking the tablets) and therefore, our estimates of adherence and compliance may be inflated. However, there was no difference between groups in reported adherence to, and discontinuation of, trial medication. The nature and degree of adjunctive rehabilitation was not documented because that would have added complexity and potential measurement error to this pragmatic trial. However, all patients were admitted to stroke units where organised interdisciplinary assessment, and rehabilitation as required, was provided as standard practice. The nature and intensity of all rehabilitation interventions were likely to be balanced between the treatment groups, in the same way that all baseline variables were balanced between groups, due to the randomisation process and double-blind trial treatment allocation. There was a slight difference in ascertainment of mRS status at 6 months between groups (fluoxetine n=624, 97.2% vs placebo n=632, 99.0%) but sensitivity analyses using imputations led to consistent conclusions. Our primary measure of efficacy was a broad measure of functional outcome which may not be sensitive to changes in measures of specific neurological functions, However, we also measured 11 domains of the SIS, including measures of motor function (strength, hand ability, mobility), physical function, and daily activities, and found no effect of fluoxetine on any of these measures. The mRS may be less sensitive to change in patients with less severe stroke but there was no evidence of an effect of fluoxetine on the mRS in patients with more severe stroke (NIHSS > 5; appendix figure 2, p15), and no effect of fluoxetine on any secondary outcome except mood and emotional control.

The AFFINITY trial was smaller than the FOCUS trial[9] but both trials recruited patients of similar stroke severity (median NIHSS=6) and at a similar time (one week, mean) after stroke onset. The AFFINITY trial population was a unique mix of Vietnamese (n=727, 57%) and Australasians (n=553, 43%), whereas the FOCUS population was predominantly Caucasian (n=2988; 96%). Patients in AFFINITY were also younger (mean age 64 years AFFINITY, vs 71 years in FOCUS), and more likely to be married (n=926, 72% vs n=1725, 55%), living with someone else (n=1120, 87% vs n=2091, 67%), employed (n=531, 41% vs n=691, 22%), and independent before their stroke (n=1264, 99% vs n=2866, 92%) compared to FOCUS. Adherence to trial medication was higher in AFFINITY than FOCUS; 34 (5.4%) patients assigned fluoxetine and 30 (4.8%) placebo stopped trial medication within the first 90 days, whereas in FOCUS, 143 (9%) patients assigned fluoxetine and 122 (8%) placebo stopped trial medication within the first 90 days. Despite these differences, the results of the AFFINITY

trial almost replicate those of the larger FOCUS trial,[9] supporting the internal and external validity of both trials. Furthermore, the EFFECTS trial of fluoxetine vs placebo in 1500 stroke patients in Sweden also reports very similar results to FOCUS and AFFINITY.[13] Moreover, the results of the FOCUS, AFFINITY and EFFECTS trials are all consistent with the totality of evidence from all RCTs of SSRIs for stroke recovery,[26] and all RCTs specifically testing fluoxetine.[27] Collectively, these trials provided compelling evidence that fluoxetine does not improve functional recovery after stroke.

The outstanding inconsistency among all the RCT evidence is the FLAME trial, which did report a significant benefit of fluoxetine vs placebo on functional recovery measured by the mRS.[5] The FLAME trial differed from AFFINITY, FOCUS and EFFECTS in that it was a phase II trial of fluoxetine 20 mg daily vs placebo in a highly select population of 113 patients with a moderate to severe hemiparesis or hemiplegia, defined by a Fugl-Meyer motor scale (FMMS) score $\leq$55.[5] The FMMS motor score ranges from 0 (hemiplegia) to a maximum of 100 points (normal motor performance), divided into 66 points for the upper extremity and 34 points for the lower extremity. At baseline, there was some imbalance between the treatment groups; the mean total FMMS score was higher (better motor performance) in the fluoxetine group (17·1; SD 11·7) than placebo group (13·4; SD 8·8), and the mean total NIHSS was marginally lower (less severe stroke) in the fluoxetine group (12·8; SD 3·9) than placebo group (13·1; SD 4·3).[5] Somatosensory and other neurological deficits that may influence recovery were not reported. The primary outcome measure, the mean change in FMMS scores between randomisation and day 90, was greater with fluoxetine than placebo (34·0 points fluoxetine vs 24·3 points placebo; difference 9.8 points, 95%CI: 3.4 to 16.1, p=0·003). The proportion of functionally independent patients (mRS scores 0-2) at day 90 was also higher with fluoxetine than placebo (n=15, 26% vs n=5, 9%; p=0.02). The FLAME trial result may be a false-positive due to random error (chance), as only 57 patients were treated with fluoxetine and followed-up to 90 days,[5] and there is large variation in spontaneous motor recovery after acute stroke.[28] Alternatively, the FLAME trial result may a true-positive, and fluoxetine may indeed improve recovery of motor function in patients with severe motor impairment. The AFFINITY trial did not include a large number patients with severe hemiparesis and did not measure motor recovery by the FMMS, but did measure motor functions as domains within the SIS and found no effect of fluoxetine. Our planned individual patient data meta-analysis of the FOCUS, AFFINITY and EFFECTS trials[8] will constitute a larger number of stroke patients with severe

motor impairments and promises to enable a more reliable analysis of the effect of fluoxetine, vs placebo, on the mRS and motor domains of the SIS at 6 months in this subgroup.

The AFFINITY trial also confirms the FOCUS trial finding that long-term fluoxetine in stroke patients has hazards, increasing the risk of bone fractures.[9] We also found that fluoxetine significantly increased the risk of falls with injury and epileptic seizures in stroke patients. These hazards of fluoxetine were sought *apriori* during patient follow-up.[7,8] The FOCUS trial reported similar, but not significant, increases in falls with injury and seizures in patients allocated fluoxetine.[9] The AFFINITY and FOCUS trials collectively provide robust evidence about the effect of an SSRI on the incidence of falls causing injury, and fractures, increasing the absolute risk of each by about 2% over 6 months among patients with recent stroke.

Although fluoxetine is more effective than placebo in treating major depressive disorders,[10] and reduced the rate of new depression in the FOCUS,[9] and other trials,[27,29] we observed only improved mood and emotional control, as measured by the SIS, at 6 months with fluoxetine; the numerically lower rate of post-stroke depression with fluoxetine vs placebo was not statistically significant. We believe we lacked statistical power to show a significant effect of fluoxetine on post-stroke depression because the absolute rates of depression in both groups in AFFINITY were substantially lower (less than half) than in FOCUS, possibly from under-reporting, particularly in Vietnam where the reporting of changes in mood may be affected by the cultural setting.[30]

In summary, the AFFINITY trial reinforces the conclusion of a recent Cochrane review that SSRIs are not effective at improving functional recovery after stroke. It also confirms that fluoxetine may improve mood but have important adverse effects, particularly bone fractures. A planned individual patient data meta-analysis of the AFFINITY, FOCUS and EFFECTS trials will produce greater precision in the estimates of the effects of fluoxetine on recovery in important patient subgroups.[8]

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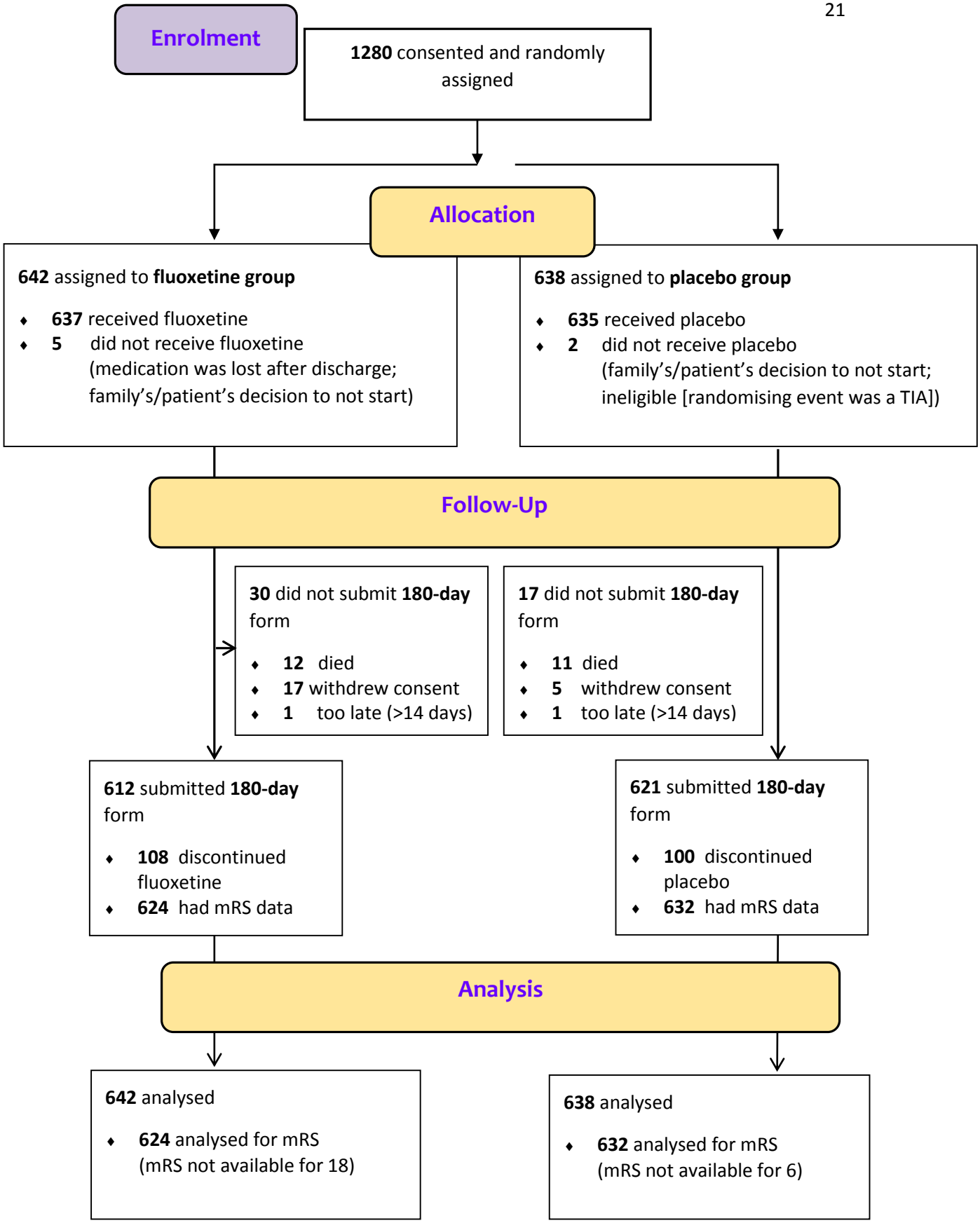
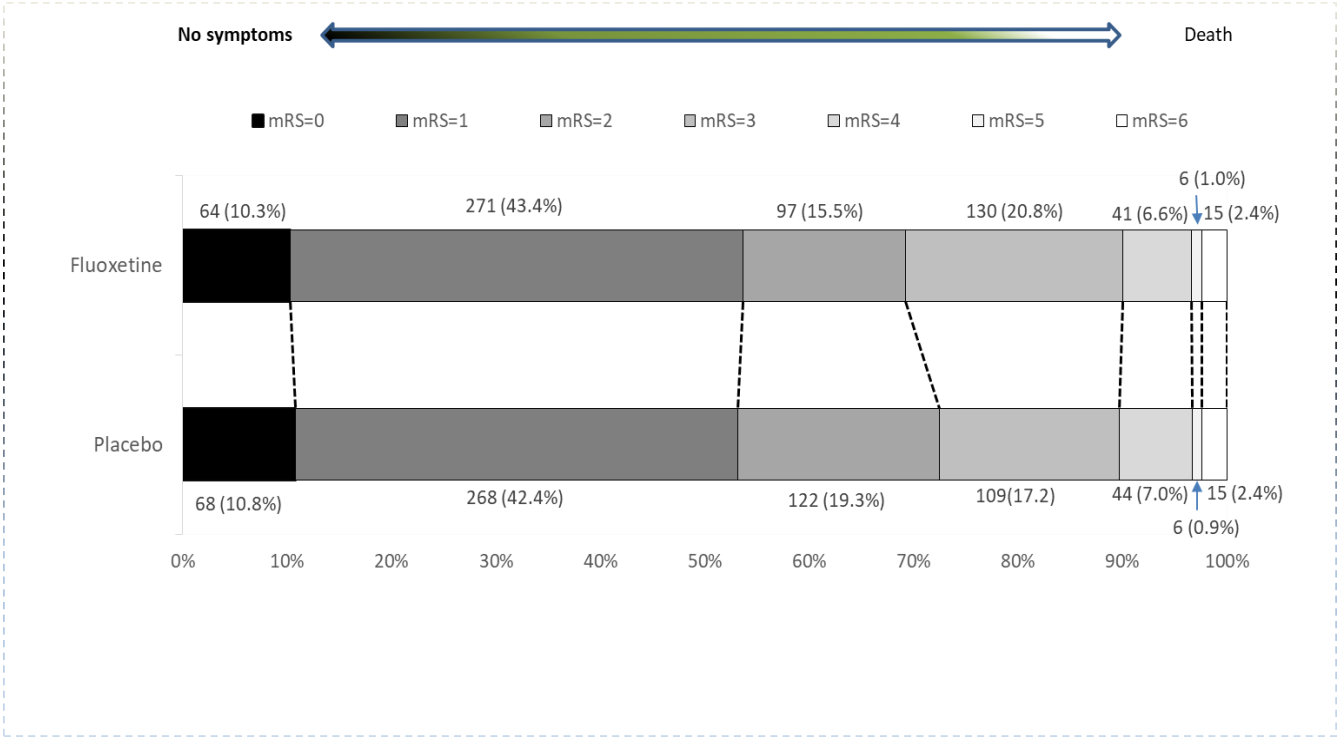


Figure 1: AFFINITY trial profile mRS=modified Rankin Scale

Figure 2.

Primary outcome of the distribution of the modified Rankin Scale (mRS) scores at 6 months by treatment group.

The primary outcome was an assessment of scores across all seven categories of the mRS (ranging from 0 [no symptoms] to 6 [death]), using a shift analysis of the ordinal data. The odds ratio and p-values were calculated with ordinal logistic regression, adjusted for the baseline variables included in the minimisation algorithm (delay between stroke onset and randomization, probability of being alive and independent at 6 months, presence of a motor deficit, presence of aphasia). mRS data at 6 months were available for 624 (97.2%) patients allocated fluoxetine and 632 (99.1%) allocated placebo. The common odds ratio was 0.936 (95%CI: 0.762 to 1.150), p= 0.53; adjusted for baseline minimization variables. A common OR less than 1.0 favoured placebo.



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GJH was Chief Investigator A of the NHMRC Project Grant 1059094, Co-Chair of the steering committee, Chair of the trial coordinating committee, involved in the design of the trial, recruited and followed-up patients enrolled at his hospital site, adjudicated all adverse and serious adverse events in the trial (blind to treatment allocation), and wrote the first and final versions of the manuscript.

MLH was Chief Investigator B of the NHMRC Project Grant 1059094, Co-Chair of the steering committee, involved in the trial design, and advised on management of the trial.

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VM (deceased December 2014) was an Associate Investigator of the NHMRC Project Grant 1059094, participated in the steering committee as CI of the EFFECTS trial, and was involved in the trial design.

EL participated in the steering committee as CI of the EFFECTS trial, and was involved in the trial design.

CSA was an Associate Investigator of the NHMRC Project Grant 1059094, participated in the steering committee, was involved in the trial design, and provided trial strategic advice.

JG was national coordinator for New Zealand, the Principal Investigator responsible for recruitment and follow-up of patients enrolled at his hospital site, and commented on the draft manuscript.

H T-N was national coordinator for Vietnam, and the Principal Investigator responsible for recruitment and follow-up of patients enrolled at his hospital site.

QY undertook the statistical analysis of the trial data for the Data Monitoring Committee meetings and for the final results.

The contributions other members of the AFFINITY trial collaboration are listed in the appendix (pp1-7).

Declaration of interests

Prof. Hankey reports grants from the National Health & Medical Research Council of Australia, Vetenskapsrådet (The Swedish Research Council), and United Kingdom National Institute for Health Research Technology (NIHR), during the conduct of the study; and personal fees from American Heart Association, outside the submitted work.

Prof. Hackett reports grants from National Health and Medical Research Council during the conduct of the study.

Prof. Etherton-Beer reports grants from National Health and Medical Research Council (NHMRC) of Australia, during the conduct of the study.

Prof. Billot reports grants from NHMRC during the conduct of the study.

Dr. Lung reports grants from Australian National Health and Medical Research Council, during the conduct of the study.

Prof. Anderson reports grants from National Health and Medical Research Council (NHMRC) of Australia, grants from Takeda, personal fees from Takeda, outside the submitted work.

Profs Almeida, Flicker, Mead, Dennis, Ford, Billot, Jan, Lundström, Thang-Nguyen, Gommans, and Yi report nothing to disclose.

Data sharing

The trial protocol and statistical analysis plan have been published.[7,8] A fully anonymised trial dataset with individual patient data and a data dictionary will be available to other researchers after the publication of the full trial results from the final follow-up at 12 months. Written proposals and requests are to be directed to Graeme Hankey (Co-Chief Investigator). Proposals will be assessed by the AFFINITY trial Steering Committee and a data sharing agreement established if, and before, any data are to be shared.

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Table 1. Patient characteristics at randomization by allocated treatment

	Fluoxetine (n=642)	**Placebo (n=638)**
Sex		
Women	231 (36%)	245 (38%)
Men	411 (64%)	393 (62%)
Age		
Age ≤ 70 years	450 (70%)	432 (68%)
Age >70 years	192 (30%)	206 (32%)
Mean age, years	63.5 (12.5)	64.6 (12.2)
Ethnicity		
Asian	356 (55%)	371 (58%)
White	267 (42%)	255 (40%)
Other	19 (3%)	12 (2%)
Marital status		
Married	463 (72%)	463 (73%)
Partner	29 (4%)	19 (3%)
Divorced or separated	37 (6%)	46 (7%)
Widowed	61 (9%)	70 (11%)
Single	52 (8%)	38 (6%)
Other	0 (0%)	2 (0%)
Living arrangements		
Living with someone else	564 (88%)	556 (87%)
Living alone	78 (12%)	78 (12%)
Living in an institution	0 (0%)	2 (0%)
Other	0 (0%)	2 (0%)
Employment status		
Full-time employment	206 (32%)	180 (28%)
Part-time employment	77 (12%)	68 (11%)
Retired	315 (49%)	363 (57%)
Unemployed or disabled	24 (4%)	14 (2%)
Other	20 (3%)	13 (2%)
Independent before stroke	634 (99%)	630 (99%)
Previous medical history		
Coronary Heart Disease	58 (9%)	57 (9%)
Ischaemic stroke or TIA	77 (12%)	84 (13%)
Diabetes	143 (23%)	147 (23%)
Hyponatraemia	1 (0%)	3 (0%)
Intracranial bleed	11 (2%)	8 (1%)
Upper gastrointestinal bleed	11 (2%)	15 (2%)
Bone fractures	71 (11%)	74 (12%)
Depression	30 (5%)	20 (3%)
Stroke diagnosis		
Non-stroke (final diagnosis)	3 (0%)	1 (0%)
Ischaemic stroke	549 (86%)	542 (85%)

Intracerebral haemorrhage	90 (14%)	95 (15%)
OCSP classification of Ischaemic stroke		
Total anterior circulation infarct	47 (9%)	50 (9%)
Partial anterior circulation infarct	271 (49%)	283 (52%)
Lacunar infarct	115 (21%)	105 (19%)
Posterior circulation infarct	114 (21%)	103 (19%)
Uncertain	2 (0%)	1 (0%)
Causes of ischaemic stroke (modified TOAST classification)		
Large artery disease	123 (22%)	134 (25%)
Small vessel disease	261 (47%)	250 (46%)
Embolism from the heart	95 (17%)	93 (17%)
Another cause	9 (2%)	8 (1%)
Unknown or uncertain cause	61 (11%)	57 (10%)
Predictive variables		
Able to walk at time of randomisation	282 (44%)	279 (44%)
Able to lift both arms off bed	443 (69%)	431 (68%)
Able to talk and not confused	554 (86%)	557 (87%)
Predicted 6-month outcome based on SSV		
Probability of being alive and independent	0.57 (0.26-0.87)	0.55 (0.24-0.87)
0.00 to $\leq$ 0.15	100 (15%)	103 (16%)
0.15 to 1.00	542 (84%)	535 (84%)
Neurological deficits		
NIHSS	6 (3-9)	6. (3-9)
Presence of a motor deficit	557 (87%)	548 (86%)
Presence of aphasia	129 (20%)	121 (19%)
Depression at baseline		
Current diagnosis of depression (patient or proxy reported)	15 (2%)	17 (3%)
Taking a non-SSRI antidepressant	5 (1%)	5 (1%)
Current mood		
PHQ-9, median (IQR)	4 (1-7)	4 (2-7)
0-14	601 (98%)	596 (98%)
$\geq$15	12 (2%)	11 (2%)
Delay (days) since stroke onset at randomisation		
Mean delay	6.1 (3%)	6.3 (3%)
2-8 days	486 (76%)	479 (75%)
9-15 days	156 (24%)	159 (25%)
Consent		
Patient consented	345 (54%)	328 (51%)
Person responsible consented	284 (44%)	295 (46%)
Proxy consented	3 (0%)	1 (0%)
Waiver acknowledgement	10 (2%)	14 (2%)

Data are n (%), mean (SD [standard deviation]), or median (IQR [interquartile range])
TIA: transient ischaemic attack
OCSP = Oxfordshire Community Stroke Project
TOAST = modified Trial of ORG 10172 in acute stroke treatment criteria
SSV = Six simple variables the predict functional outcome, as measured by the mRS, after stroke (age, living alone before the stroke, independent in activities of daily living before the stroke, and able to talk, lift both arms off the bed, and walk unassisted at the time of randomisation).[15]
NIHSS = National Institutes of Health Research Stroke Scale
SSRI: selective serotonin reuptake inhibitor
PHQ-9 = Patient Health Questionnaire 9 items (higher scores indicate more depressive symptoms).[17]

Table 2. Secondary outcomes at six months by allocated treatment

	Fluoxetine (n=642)		Placebo (n=638)		P value
New depression N / N (%)	33 (5.1%)		46 (7.2%)		0.13
Mood (PHQ-9)	2.0	(1.0-5.0)	2.0	(1.0-5.0)	0.42
PHQ-9 ≥15 N / N%	4 (0.7%)		6 (1.0%)		0.75
Cognition (TICSm)	24.0	(20.0 -27.0)	24.0	(19.0-27.0)	0.62
Stroke Impact Scale (SIS) domains					
-Strength	75.0	(56.3-93.8)	75.0	(56.3-93.8)	0.26
-Hand ability	85.0	(55.0-100.0)	85.0	(55.0-100.0)	0.39
-Mobility	91.7	(69.4-100.0)	88.9	(66.7-97.2)	0.08
-Motor†	83.5	(63.5-94.2)	82.4	(60.4-93.2)	0.28
-Daily Activities	90.0	(72.5-100.0)	90.0	(70.0-97.5)	0.25
-Physical function‡	85.5	(66.2-94.9)	83.8	(63.4-93.8)	0.24
-Memory	89.3	(78.6-100.0)	89.3	(75.0-100.0)	0.28
-Communication	98.2	(89.3-100.0)	96.4	(85.7-100.0)	0.61
-Mood/Emotions^	80.6	(66.7 -88.9)	77.8	(66.7 -86.1)	0.003
-Participation	81.3	(59.4 -96.9)	75.0	(56.3 -96.9)	0.48
-Recovery (VAS)	80.0	(60.0 -90.0)	80.0	(60.0 -90.0)	0.90
Vitality (SF-36)	70.0	(55.0 -80.0)	70.0	(55.0 -80.0)	0.36
EQ5D-5L	0.81	0.63-1.00	0.78	0.58-0.93	0.08

Data were only available for those who survived and who completed sufficient questions to derive a score. The number of patients with missing scores were similar in the two treatment groups.

Data are median (IQR).

PHQ-9: Patient Health Questionnaire 9 items (higher score indicates more depressive symptoms)

TICSm: Telephone Interview for Cognitive Status

SIS: Stroke Impact Scale (where higher scores are better).

†Mean of the Strength, Hand ability, and Mobility domains.

‡Mean of the Strength, Hand ability, Mobility, and Daily activities domains.

^Mood/Emotions domain of the SIS: Nine questions about "how you feel, changes in your mood, and your ability to control your emotions, since your stroke." (where higher scores are better)

VAS: visual analogue scale.

SF-36: 36 item short form questionnaire (higher scores indicate less disability)

EQ5D-5L: EuroQoL - 5 Dimensions (Mobility, Personal Care, Usual Activities, Pain/Discomfort, Anxiety/Depression) - 5 Levels (where 1 indicates the best health imaginable, and −0.676 indicates the worst health imaginable).

Table 3. Adverse events at 6 months by allocated treatment group

	Fluoxetine (n=642)	**Placebo (n=638)**	**Difference (95% CI)***	**P-value**
Death	15 (2.34%)	15 (2.35%)	0.01% (-1.64 to 1.67)	1.00
Any stroke	18 (2.80%)	26 (4.08%)	-1.27% (-3.27 to 0.72)	0.22
All thrombotic events				
Ischaemic stroke	11 (1.71%)	21 (3.29%)	-1.58% (-3.29 to 0.13)	0.08
Acute coronary events	1 (0.16%)	2 (0.31%)	-0.16% (-0.69 to 0.37)	0.62
All bleeding events				
Haemorrhagic stroke	3 (0.47%)	1 (0.16%)	0.31% (-0.30 to 0.92)	0.62
Upper gastrointestinal bleed	1 (0.16%)	1 (0.16%)	0.00% (-0.43 to 0.43)	1.00
Epileptic seizures	10 (1.56%)	2 (0.31%)	1.24% (0.19 to 2.30)	0.04
Fall with injury	20 (3.12%)	7 (1.10%)	2.02% (0.45 to 3.59)	0.02
New bone fracture	19 (2.96%)	6 (0.94%)	2.02% (0.51 to 3.53)	0.01
Hyponatraemia < 125mmol/l	3 (0.47%)	2 (0.31%)	0.15% (-0.53 to 0.84)	1.00
Hyperglycaemia	0 (0%)	0 (0%)	0%	
Symptomatic hypoglycaemia	0 (0%)	0 (0%)	0%	
New depression	33 (5.14%)	46 (7.21%)	-2.07% (-4.71 to 0.57)	0.13
New antidepressant	30 (4.67%)	43 (6.74%)	-2.07% (-4.61 to 0.47)	0.12
Attempted or actual suicide	0 (0%)	2 (0.31%)	-0.16% (-0.75 to 0.12)	0.25
Other adverse event	62 (9.66%)	68 (10.66%)	-1.00% (-4.31 to 2.31)	0.56

Data are n (%), unless otherwise stated

* Risk differences and their 95%confidence intervals were calculated in SAS by means of the FREQ procedure. https://documentation.sas.com/?docsetId=procstat&docsetTarget=procstat_freq_details54.htm&docsetVersion=9.4&locale=en (accessed March 18, 2020). The confidence intervals around the risk differences are Wald intervals based on the normal approximation.

Supplementary Appendix

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Investigational Medicinal Product

Manufactured by Siegfried Malta Ltd (fluoxetine, certificate MT/008HM/2017) and Pharmaceutical packaging professionals (PPP) Pty Ltd (placebo)

Packaged by Amneal Pharmaceuticals Pty Ltd (Australian Therapeutic Goods Administration [TGA] licence holder).

Re-packaged (as patient kits, two bottles, each containing 110 capsules), labelled (with trial-specific treatment codes, fluoxetine or placebo), and distributed by PPP Pty Ltd.

Export to New Zealand and Vietnam approved by the Australian Government Department of Health TGA (Approval Ref No: EX17/336513).

Funding

National Health and Medical Research Council, Australia

Registration

Australian New Zealand Clinical Trial Registry number: ACTRN12611000774921

Sponsors

Royal Perth Hospital and Sir Charles Gairdner Hospital, Perth, Western Australia

Participating centres and number of patients randomised in each treatment group.

The participating centres are grouped by the highest to lowest recruiting country, followed by highest to lowest recruiting site. If centres have equal recruiting numbers, the sites are listed by alphabetical order. We have listed each centre by site number and name with the total number of patients recruited in [n], followed by names of the local principal investigator(s), and other significant contributors in that centre.

Vietnam [706 patients recruited]

Nguyen Tri Phuong Hospital [179] ((Tran Trung Thanh (PI), Le Tran Truc Mai Loan, Kieu Le Vu Thuy, Nguyen Van Sang, Nguyen Anh Diem Thuy, Dang Nhat Tam);

The Peoples Hospital 115 [110] (Nguyen Huy Thang (PI), Truong Le Tuan Anh, Dam Thi Cam Linh, Bui Thi Quynh Chau, Ngo Thi Kim Trinh, Pham Nguyen Thanh Thai, Luong Van Dong, Doan Van Tan, Ma Hoa Hung, Pham Nguyen Binh, Phan Dang Loc, Dao Thi Thanh Nha, Nguyen Thi Bich Huong, Le Thi Cam Linh, Do Minh Chi, Huynh Quoc Huy, Nguyen Quoc Trung, Nguyen Thanh Thai An);

Nghe An General Friendship Hospital [100] (Duong Dinh Chinh (PI), Kieu Van Duong, Le Na, Nguyen Ngoc Hoa, Le Van Binh, Nguyen Thanh Long);

Gia Dinh Peoples Hospital [79] (Vo Van Tan (PI), Bui Ngoc Tram, Hoang Thi To Uyên, Nguyen Thi Bich Hien, Nguyen Thi Thu Ha, Lam Thuy Nga, Le Kim Khanh, Trinh Thanh Phuong);

Thanh Hoa General Hospital [63] (Nguyen Hoanh Sam (PI), Le Hong Ninh, Nguyen Truong Giang, Doan Thi Bich, Pham Phuoc Sung, Luong Huu Duong, Mai Van Ha);

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Cho Ray Hospital [33] (Nguyen Anh Tai (PI), Le Van Tuan, Truong Van Luyen, Bui Chau Tue, Tran Van Nhat, Huynh Xuan Ngọc, Dinh Van Lap, Pham Gia An, Nguyen Tuong Vy);

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Australia [532 patients recruited]

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Liverpool Hospital, NSW, [22] (Dennis Cordato (PI), Alan J McDougall, Cecilia Cappelen-Smith, Zeljka Calic, Shabeel Askar, Qi Cheng, Raymond Kumar);

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Prince of Wales, NSW, [4] (Pesi Katrak (PI) (Annie Winker PI), Alessandro Zagami, Alanah Bailey, Sarah Mccormack, Andrew Murray, Mark Rollason, Christopher Taylor);

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Caulfield Hospital, VIC, [2] (Peter New (PI), Sam Akbari, Hannah Coyle, Megan O'Neill, Diana Ramirez);

Footscray & The Sunshine Hospitals, VIC, [2] (Tissa Wijeratne (PI), Sherisse Celestino, Essie Low, Cynthia Chen, Jennifer Bergqvist);

Manly Hospital, NSW, [2] (Andrew Evans (PI) Queenie Leung);

Wagga Wagga Base Hospital, NSW, [1] (Martin Jude (PI), Rachael McQueen, Katherine Mohr, Latitia Kernaghan);

Flinders Medical Centre, SA, (Andrew Lee (PI), Paul Stockle, Boon Loong Tan, Sara Laubscher);

Australian participating States Abbreviation Key:

NSW = New South Wales

QLD = Queensland

SA = South Australia

VIC = Victoria

WA = Western Australia

New Zealand [42 patients recruited]

Hawke's Bay Hospital [14] (John Gommans (PI), Diana Schmid, Melissa Spooner);

Taranaki Base Hospital [14] (Bhavesh Lallu (PI), Bronwen Pepperell, John Chalissery);

Rotorua Hospital [8] (Karim Mahawish (PI), Susan DeCaigney, Paula Broughton, Karen Knight, Veronica Duque);

Wellington Hospital [6] (Harry McNaughton (PI), Jeremy Lanford, Vivian Fu, Lai-Kin Wong);

Supplementary table 1.

Methods of patient follow-up

Method of Follow-up	**Fluoxetine (n=642)**	**Placebo (n=638)**	**p-values** (A,B)
Day 28			
Outpatient Clinic	345	356	
Telephone	195	212	
Hospital	76	57	
Other (e.g. email, home visit)	20	11	
Missing	2	1	
Total submitted	638	637	0.0928 (0.1290[B])
Day 90			
Outpatient Clinic	357	360	
Telephone	233	239	
Hospital	14	6	
Other (e.g. email, home visit)	21	26	
Missing	4	0	
Total submitted	629	631	0.2848 (0.1020 [B])
Day 180			
Outpatient Clinic	295	321	
Telephone	300	287	
Other (e.g. email, home visit)	15	12	
Missing	2	1	
Total submitted	612	621	0.4410 (0.5879 [B])

A. P-values are based on the combined methods of follow-up (in-hospital assessment, outpatient clinic, telephone, home visit, and email).

B. P-values in brackets include missing data as another category.

Supplementary table 2.

Adherence to trial medication in each treatment group and overall:

temporary and permanent cessation at each follow-up

	Fluoxetine (n=642), N (%)	**Placebo (638), N (%)**	**Total (N= 1280), N (%)**	**p-value (chi-square test)**
Temporary cessation				
0-1 month	46/638 (7.2)	37/637(5.8)	83/1275(6.5)	0.3104
1-3 month	34/629(5.4)	28/631(4.4)	62/1260(4.9)	0.4270
3-6 month	19/612(3.1)	14/621(2.3)	33/1233(2.7)	0.3551
Total*	**87**	**71**	**158**	
Permanent cessation				
0-1 month	47/638(7.4)	46/637 (7.2)	93/1275 (7.3)	0.9205
1-3 month	34/629(5.4)	30/631(4.8)	64/1260 (5.2)	0.5987
3-6 month	27/612(4.4)	24/621(3.9)	50/1233(4.1)	0.6296
Total	**108**	**100**	**208**	

* Some patients reported temporary cessation of trial drug on multiple occasions.

Supplementary table 3.

Compliance with trial medication (actual dosing history compared to the prescribed drug regimen of once daily, 7 times per week) in each treatment group and overall.*

Time point **Average number of times medication taken weekly**	**Fluoxetine** **(n=642)**	**Placebo** **(638)**	**Total** **(N= 1280)** **N (%)**	**p-values**
1 month				0.5703
0 times per week	26 /630 (4.1)	25 /631 (4.0)	51 /1261 (4.0)	
1-2 times per week	16 /630 (2.5)	9 /631 (1.4)	25 /1261 (2.0)	
3-4 times per week	8 /630 (1.3)	10 /631 (1.6)	18 /1261 (1.4)	
5-6 times per week	24 /630 (3.8)	17 /631 (2.7)	41 /1261 (3.3)	
7 times per week	556 /630 (88.3)	570 /631 (90.3)	1126 /1261 (89.3)	
Missing	8	6	14	
3 months				0.9398
0 times per week	63 /622 (10.1)	62 /625 (9.9)	125 /1247 (10.0)	
1-2 times per week	6 /622 (1.0)	6 /625 (1.0)	12 /1247 (1.0)	
3-4 times per week	7 /622 (1.1)	6 /625 (1.0)	13 /1247 (1.0)	
5-6 times per week	15 /622 (2.4)	10 /625 (1.6)	25 /1247 (2.0)	
7 times per week	531 /622 (85.4)	541 /625 (86.6)	1072 /1247 (86.0)	
Missing	7	6	13	
6 months				0.9190
0 times per week	72 /608 (11.8)	76 /616 (12.3)	148 /1224 (12.1)	
1-2 times per week	5 /608 (0.8)	5 /616 (0.8)	10 /1224 (0.8)	
3-4 times per week	6 /608 (1.0)	8 /616 (1.3)	14 /1224 (1.1)	
5-6 times per week	10 /608 (1.6)	15 /616 (2.4)	25 /1224 (2.0)	
7 times per week	515 /608 (84.7)	512 /616 (83.1)	1027 /1224 (83.9)	
Missing	4	5	9	

* Proportions were calculated based on non-missing observations.

Supplementary table 4.

Results from the ordinal and binary analyses of the mRS

	Estimate (95%CI)	**p-value**
Unadjusted proportional odds model:		
Common odds ratio (OR)	0.97 (0.79 to 1.18)	0.7354
Adjusted proportional odds model*		
Common OR	0.94 (0.76 to 1.15)	0.5296
Unadjusted binary logistic regressions		
OR: 0 vs 1-6	0.95 (0.66 to 1.36)	0.7713
OR: 0-1 vs 2-6	1.02 (0.82 to 1.28)	0.8531
OR: 0-2 vs 3-6	0.86 (0.67 to 1.09)	0.2069
OR: 0-3 vs 4-6	1.04 (0.72 to 1.50)	0.8375
OR: 0-4 vs 5-6	0.99 (0.53 to 1.83)	0.9665
OR: 0-5 vs 6	0.99 (0.48 to 2.04)	0.9718

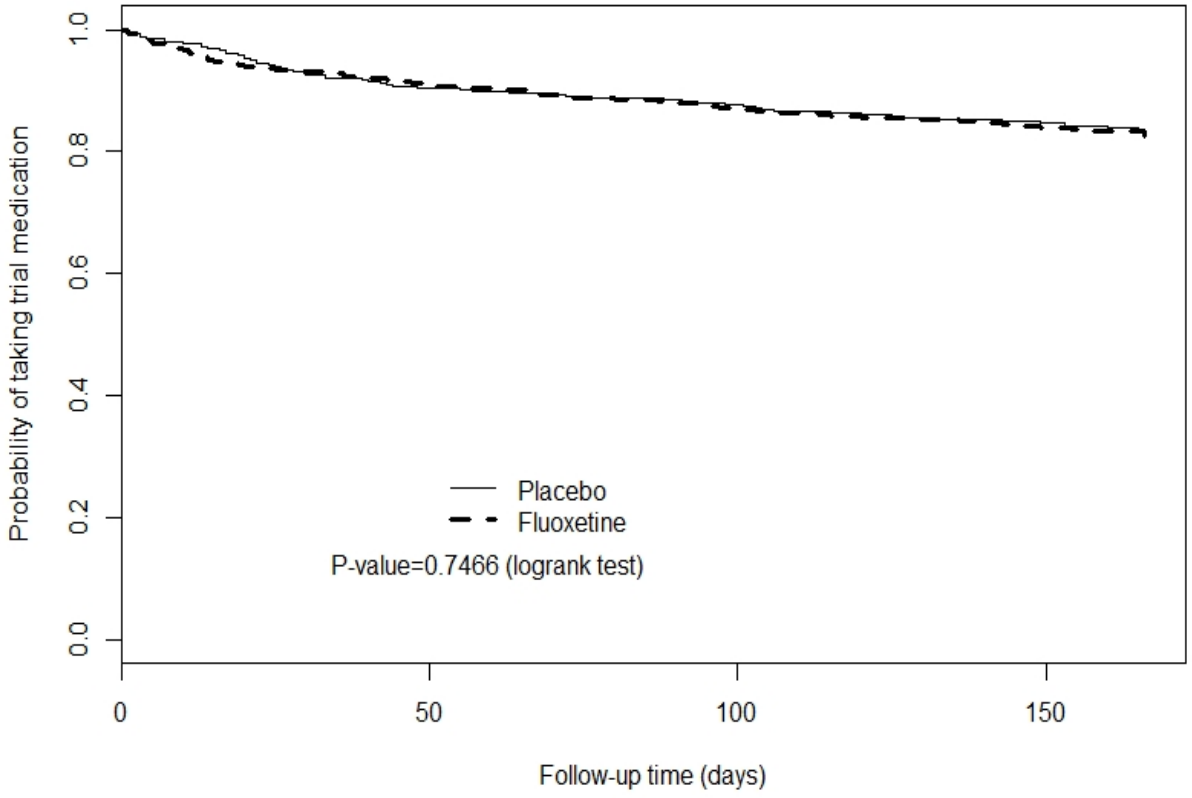
*The covariates used for the adjustment were the same as for the primary outcome analysis, that is, the analysis was adjusted for baseline minimization variables including delay since stroke onset computer-generated prediction of 6-month outcome, presence of a motor deficit and aphasia.

Supplementary table 5.

Sequential per-protocol analysis of the 1256 patients with mRS data at 6 months.

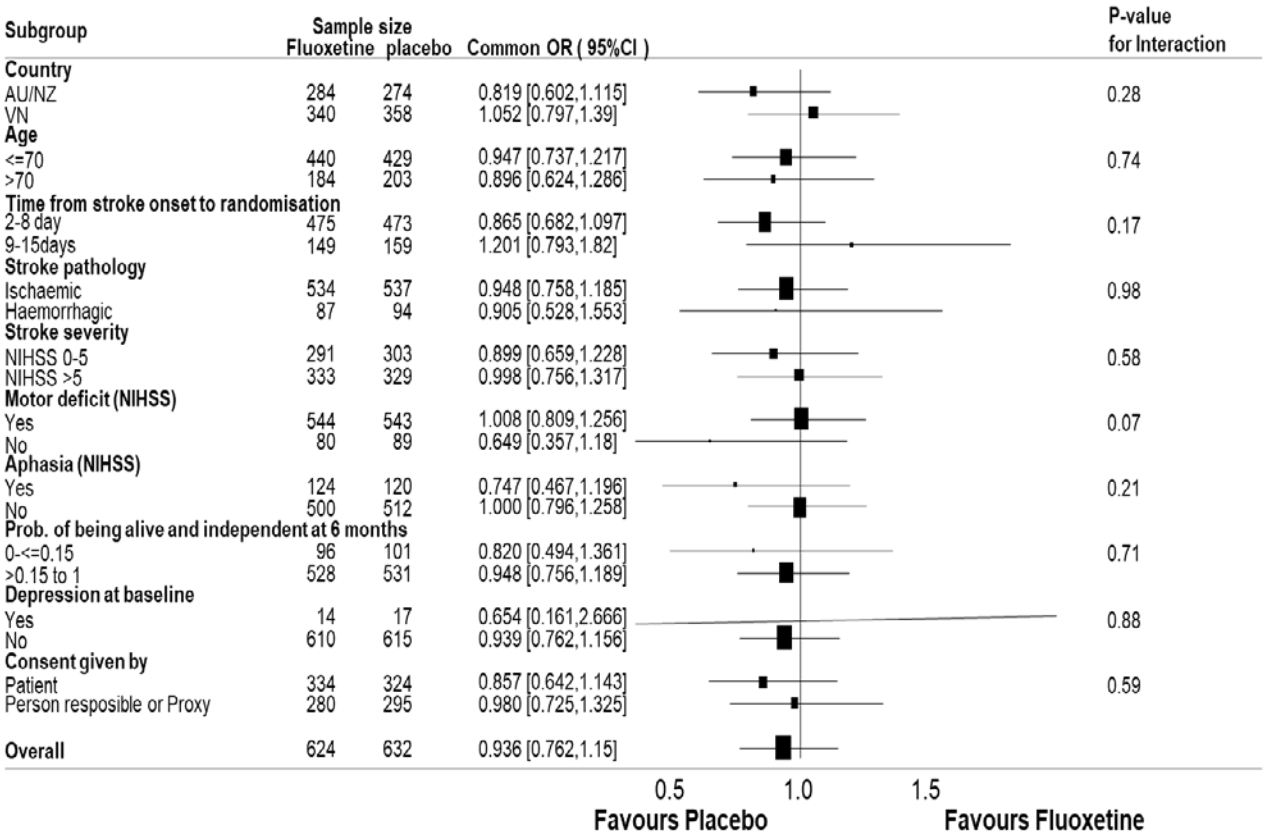
Groups cumulatively excluded	No. meeting each exclusion criteria	Cumulative no. removed from analysis	No. remaining in Fluoxetine group	No remaining in Placebo group	Common OR for mRS	95%CI	p-value	P-value (adjusted)
None –as per intention to treat analysis	0	0	624	632	0.97	0.79-1.18	0.7354	0.5296
1. Ineligible- didn't meet all inclusion criteria	4	4	621	631	0.97	0.79 -1.18	0.7354	0.5296
2. Received no trial medication	7	11	616	629	0.98	0.80 -1.20	0.8510	0.6361
3. Received <90 days of trial medication due to failure to follow trial procedures.	4	15	614	627	0.98	0.80 -1.20	0.8232	0.5413
4. Received <90 days of trial medication as chosen by patient, relative, or doctor, but not for adverse reactions.	30	45	598	613	0.97	0.79 -1.18	0.7412	0.4604
5. Received <90 days of trial medication due to suspected adverse reaction to the trial medication.	68	113	571	572	0.96	0.78 -1.17	0.6660	0.4068
6. Allocated to placebo but received an SSRI for > 10 days within the first 90 days	13	126	571	559	0.89	0.72 -1.10	0.2678	0.1309
7. Allocated to fluoxetine but received an SSRI for > 10 days within the first 90 days.	13	139	558	559	0.86	0.69 -1.06	0.1638	0.0783
8. Patients who did not complete at least 150 days of treatment	71	210	520	526	0.90	0.72 -1.11	0.3204	0.1600

This per-protocol analysis sequentially excluded subgroups of patients who either did not meet our eligibility criteria or had incomplete adherence to the trial medication, and shows the effect of fluoxetine vs placebo on the primary outcome of the mRS at 6 months for each subgroup.



Supplementary figure 1.

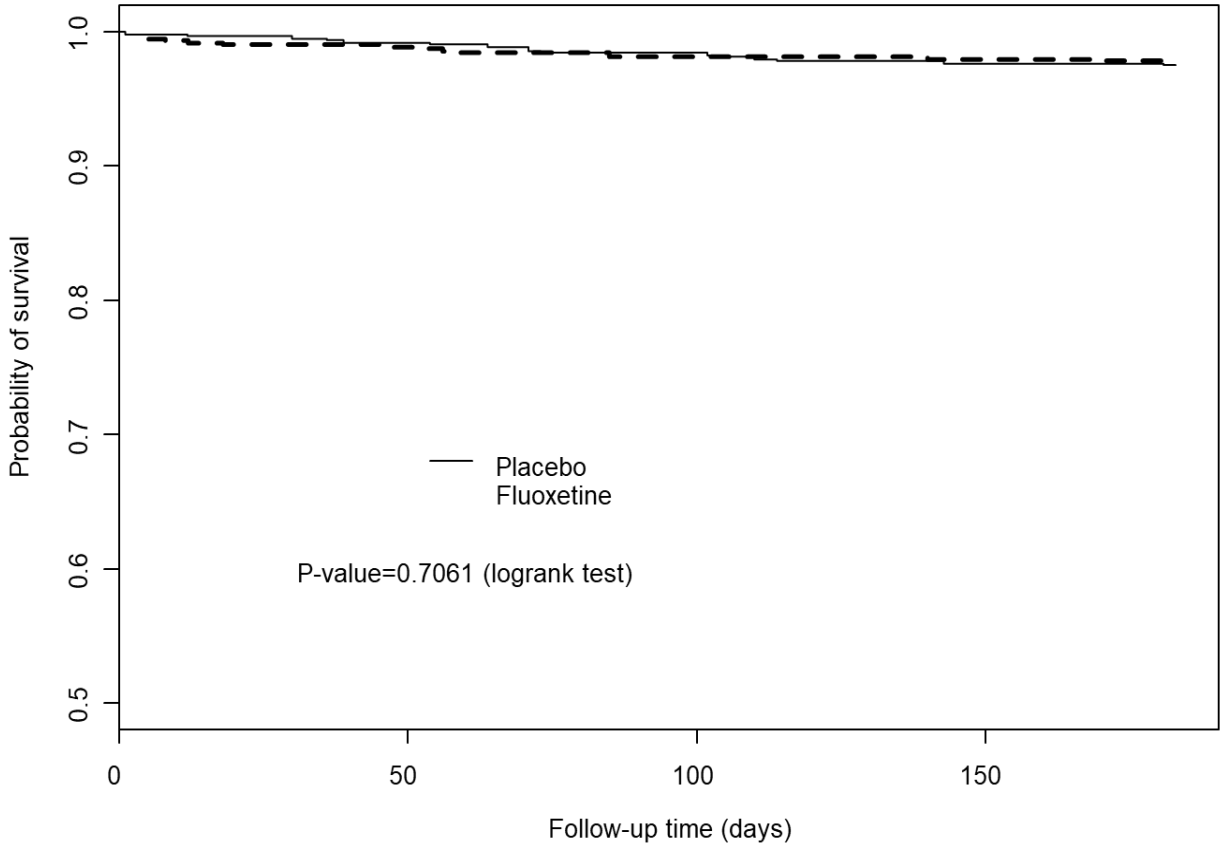
Kaplan Meier curve of time to permanent discontinuation of trial medication



Supplementary figure 2.

Primary outcome by pre-specified subgroups.

The primary efficacy outcome was shift in the modified Rankin scale score distribution (range 0 [no symptoms] to 6 [death]) at 6 months (180 days). For subcategories, black squares represent point estimates (with the area of the square proportional to the number of events), and horizontal lines represent 95% CIs. Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. Country: Country of randomization. AU/NZ: Australia, New Zealand. VN: Vietnam. NIHSS: National Institutes of Health Stroke Scale



Supplementary figure 3.

Kaplan Meier survival curve to 6 months follow-up.

Patients who withdrew consent to be followed-up were censored at the time of withdrawal from the trial.

ASSESSMENT OF FLUOXETINE IN STROKE RECOVERY (AFFINITY) TRIAL

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Ha	Thi Hai-Dinh
Khanh	Thi Ngoc-Thach
Cuong	Van-Pham
Linh	Hai-Nguyen
Phuong	Hong-Tran
Vien	Chi - Le
Tai	Anh – Nguyen
Tuan	Van – Le
Luyen	Van – Truong
Tue	Chau – Bui
Ngoc	Xuan – Huynh
Lap	Van – Dinh
An	Gia – Pham
Trang	Thi Huyen – Le
Vy	Tuong - Nguyen
Yen	Hai – Nguyen
Thang	Ba – Nguyen
Huy	Thai
Quyen	Thi Ngoc – Pham
Khoa	Duy – Dao
Quoc	Nguyen Bao – Pham
Thuong	Thi Huyen - Dang
Huong	Huynh To – Dinh
Trang	Mai – Tong
Thuy	Thi – Vu
Si	Tri – Le
Tai	Ngoc – Tran
Phuong	Hoai – Tran
Ngoc	Thuy Nhu – Dinh
Binh	Thanh-Nguyen
Vinh	Phuong-Do

Anh	Ngoc-Nguyen
Binh	Thi Thanh-Nguyen
Binh	Thanh-Nguyen
David	Blacker
Anne	Claxton
Lindsey	Bunce
Ai Ling	Tan
Darshan	Ghia
Gillian	Edmonds
Nicole	O'Loughlin
Megan	Ewing
Kerri-Ann	Whittaker
Lorralee	Deane
Darshan	Ghia
Graeme	Hankey
Anne	Claxton
Yash	Gawarikar
Brett	Jones
Maria	Lopez
Koushik	Nagesh
Emma	Siracusa
Stephen	Davis
Amy	McDonald
Jess	Tsoleridis
Rachael	McCoy
David	Jackson
Gab	Silver
Tim	Bates
Amanda	Boudville
Lynda	Southwell
Dennis	Cordato
Alan J.	McDougall
Cecilia	Cappelen-Smith
Zeljka	Calic
Shabeel	Askar
Qi	Cheng
Raymond	Kumar
Richard	Geraghty
Maree	Duroux
Megan	Ratcliffe
Samantha	Shone
Cassandra	McLennan
Ramesh	Sahathevan
Casey	Hair
Stanley	Levy
Beverley	Macdonald
Benjamin	Nham
Louise	Rigney
Dev	Nathani

Sumana	Gopinath
Vishal	Patel
Abul	Mamun
Benjamin	Trewin
Chun	Phua
Ho	Choong
Lauren	Tarrant
Kerry	Boyle
Luisa	Hewitt
Monique	Hourn
Amanda	Masterson
Kim	Oakley
Karen	Ruddell
Colette	Sanctuary
Kimberley	Veitch
Camelia	Burdusel
Lina	Lee
Gary	Cheuk
Jeremy	Christley
Tabitha	Hartwell
Craig	Davenport
Kate	Hickey
Rosanna	Robertson
Michelle	Carr
Sam	Akbari
Hannah	Coyle
Megan	O'Neill
Cameron	Redpath
Caroline	Roberts
Marjan	Tabesh
Toni	Withiel
Kapila	Abeysuriya
Andrew	Granger
Angela	Abraham
Chermaine	Chua
Dung	Do Nguyen
Vathani	Surendran
Melissa	Daines
David	Shivlal
Mudassar	Latif
Noreen	Mughal
Patricia	Morgan
Martin	Krause
Miriam	Priglinger
Ehsan E.	Shandiz
Susan	Day
Tim	Bates
Lay	Kho

Michael	Pollack
Judith	Dunne
Helen	Baines
Merridie	Rees
Jenni	White
Monique	Hourn
Kimberley	Veitch
Aicuratiya	Withanage
Colette	Sanctuary
Candice	Delcourt
Cheryl	Carcel
Alejandra	Malavera
Amy	Kunchok
Elizabeth	Ray
Elizabeth	Pepper
Emily	Duckett
Jenni	White
Kimberley	Veitch
Luisa	Hewitt
Monique	Hourn
Kerry	Boyle
Sally	Ormond
Colette	Sanctuary
Andrew	Moey
Timothy	Kleinig
Vanessa	Maxwell
Chantal	Baldwin
Wilson	Vallat
Deborah	Field
Romesh	Markus
Kirsty	Page
Danielle	Wheelwright
Sam	Bolitho
Steven	Faux
Fix	Sangvatanakul
Alexis	Brown
Susan	Walker
Jennifer	Massey
Michael	Pollack
Jenni	White
Kimberley	Veitch
Hillary	Hayes
Luisa	Hewitt
Monique	Hourn
Colette	Sanctuary
Pesi	Katrak
Annie	Winker
Alessandro	Zagami
Alanah	Bailey

Sarah	Mccormack
Andrew	Murray
Mark	Rollason
Christopher	Taylor
Fintan	O'Rourke
Ye Min	Kuang
Heike	Burnet
Yvonne	Liu
Qi	Cheng
Aileen	Wu
Sam	Akbari
Hannah	Coyle
Megan	O'Neill
Diana	Ramirez
Tissa	Wijeratne
Sherisse	Celestino
Essie	Low
Cynthia	Chen
Jennifer	Bergqvist
Andrew	Evans
Queenie	Leung
Martin	Jude
Rachael	McQueen
Katherine	Mohr
Latitia	Kernaghan
Paul	Stockle
Boon L.	Tan
Sara	Laubscher
Diana	Schmid
Melissa	Spooner
Bhavesh	Lallu
Bronwen	Pepperell
John	Chalissery
Karim	Mahawish
Susan	DeCaigney
Paula	Broughton
Karen	Knight
Veronica	Duque
Harry	McNaughton
Jeremy	Lanford
Vivian	Fu
Lai-Kin	Wong

Figures

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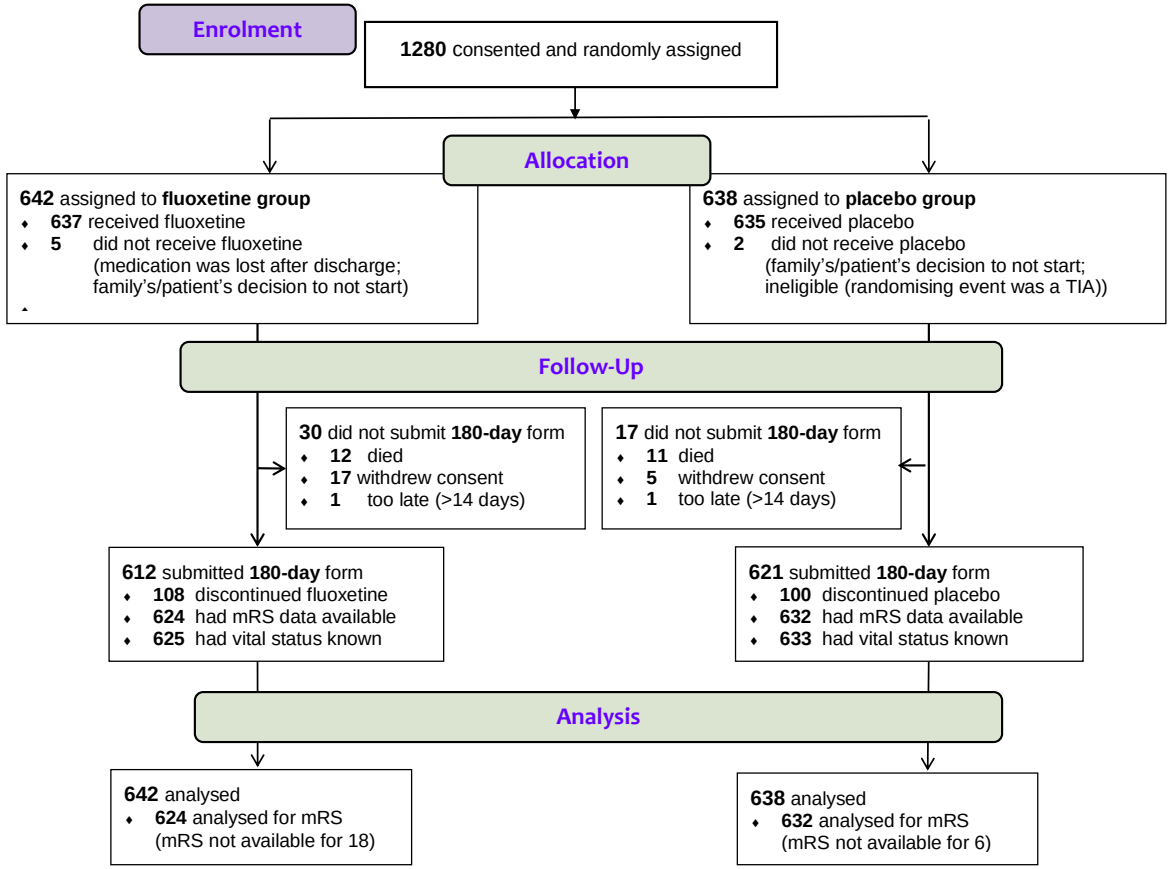


Figure 1: AFFINITY trial profile mRS=modified Rankin Scale

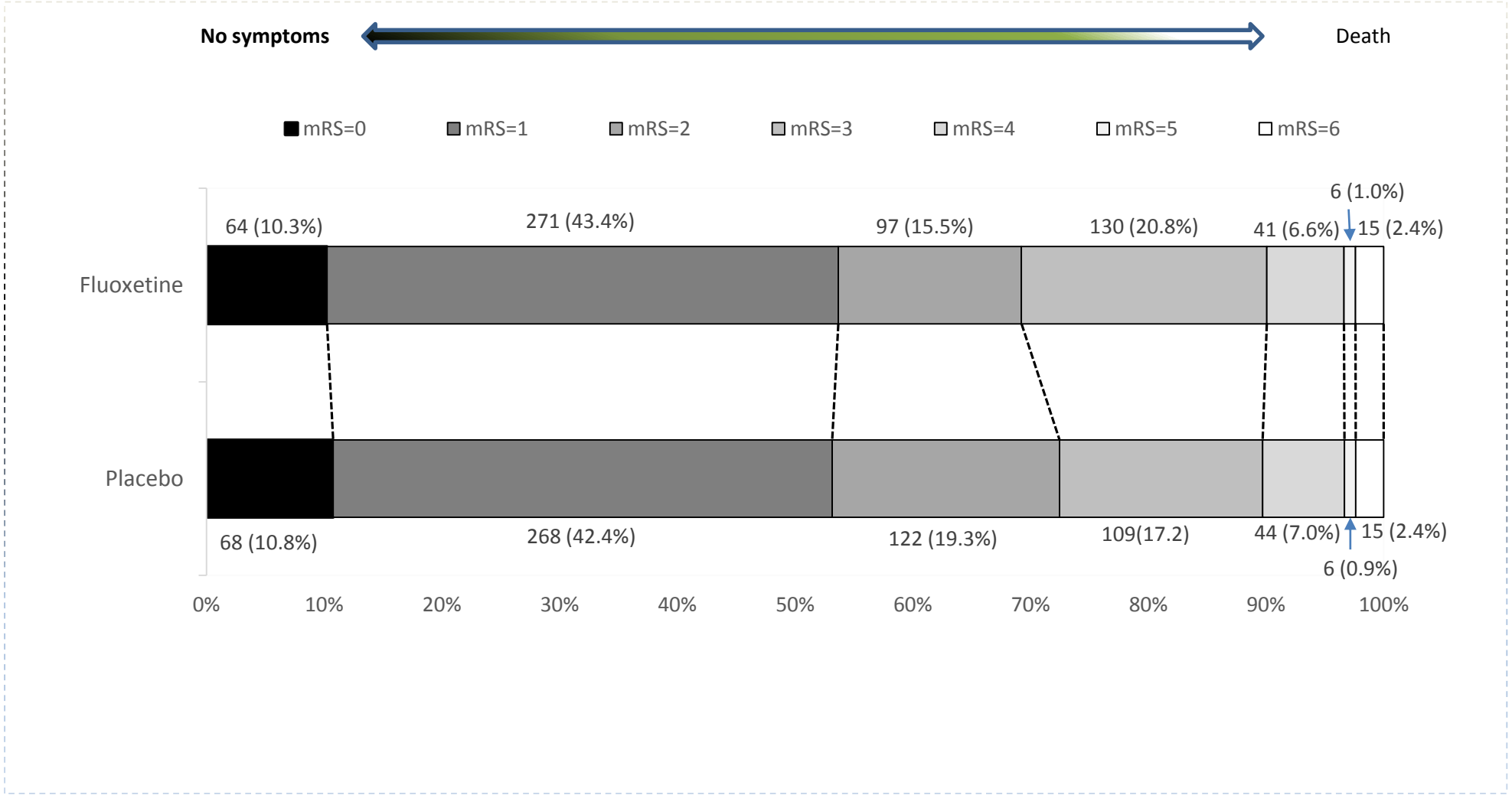
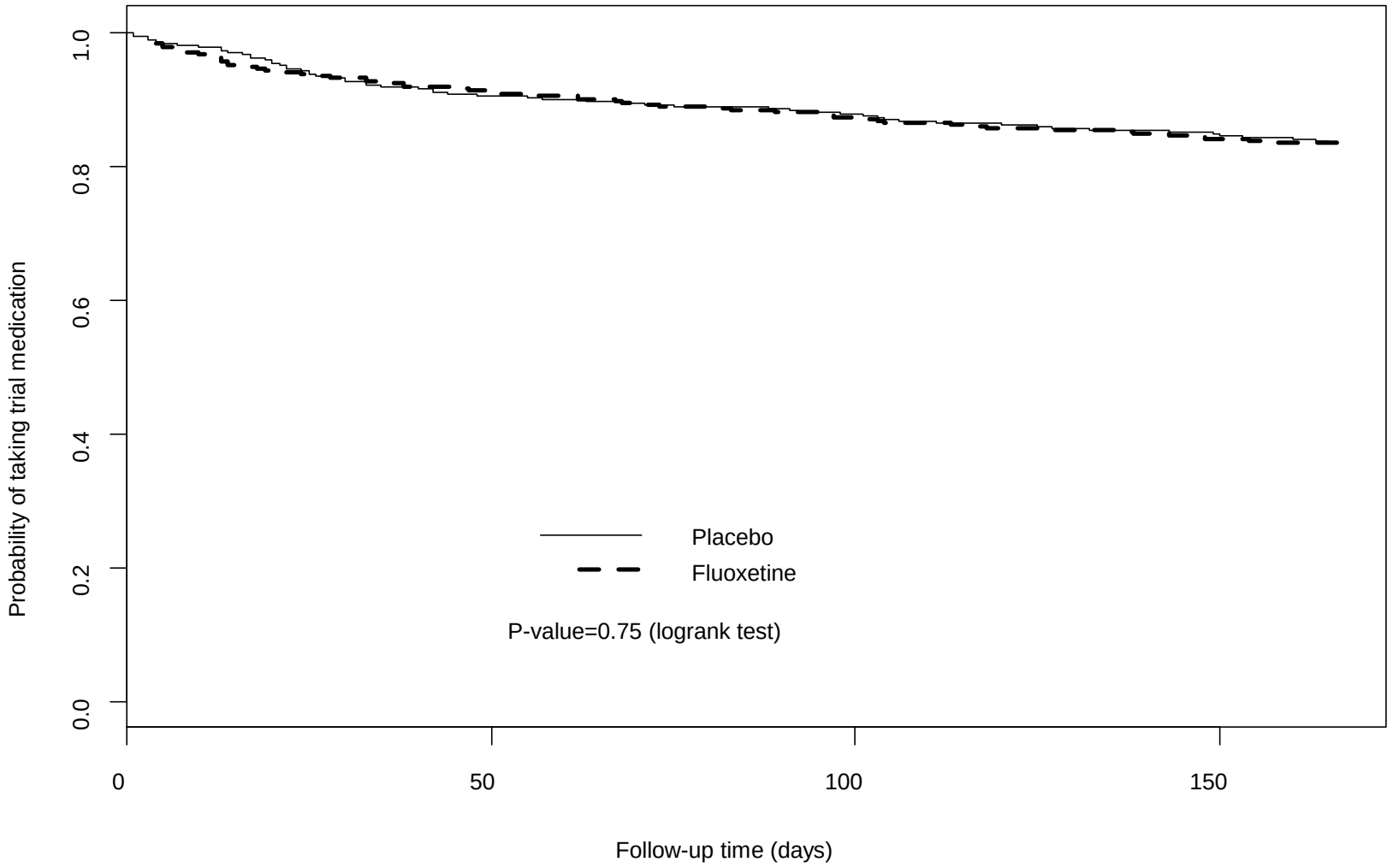
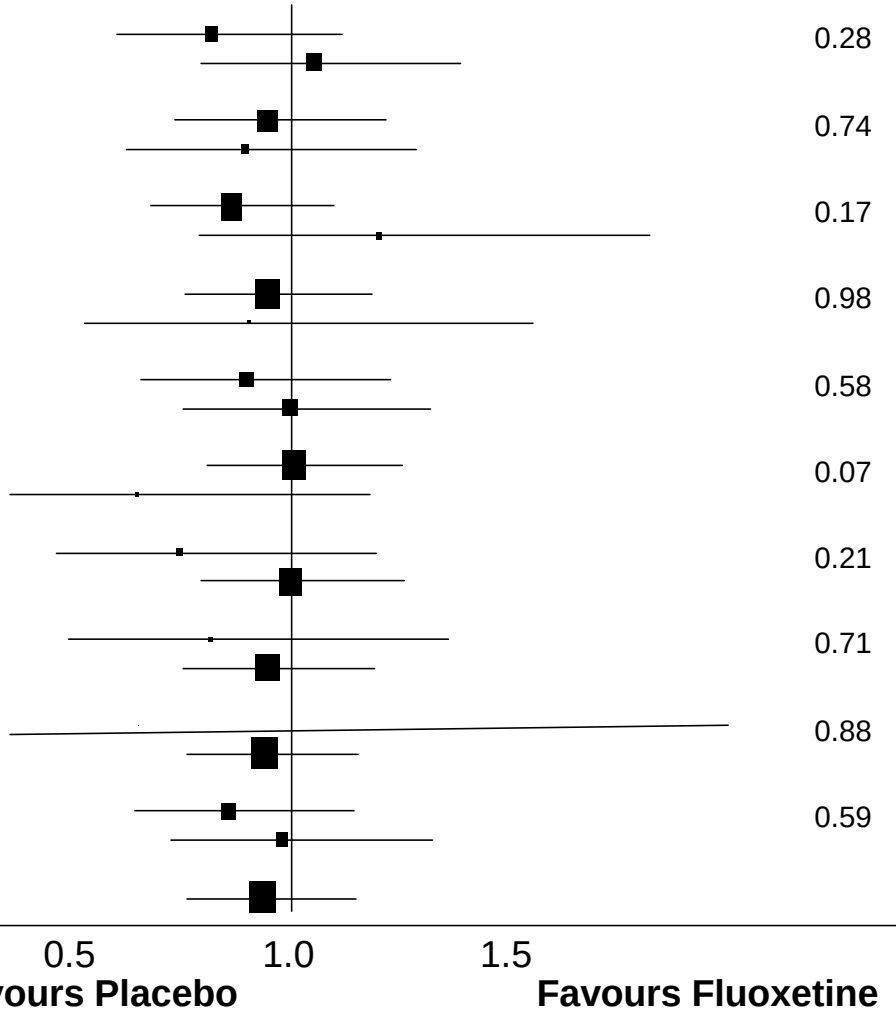


Figure 2. Primary outcome of the distribution of the modified Rankin Scale (mRS) scores at 6 months by treatment group

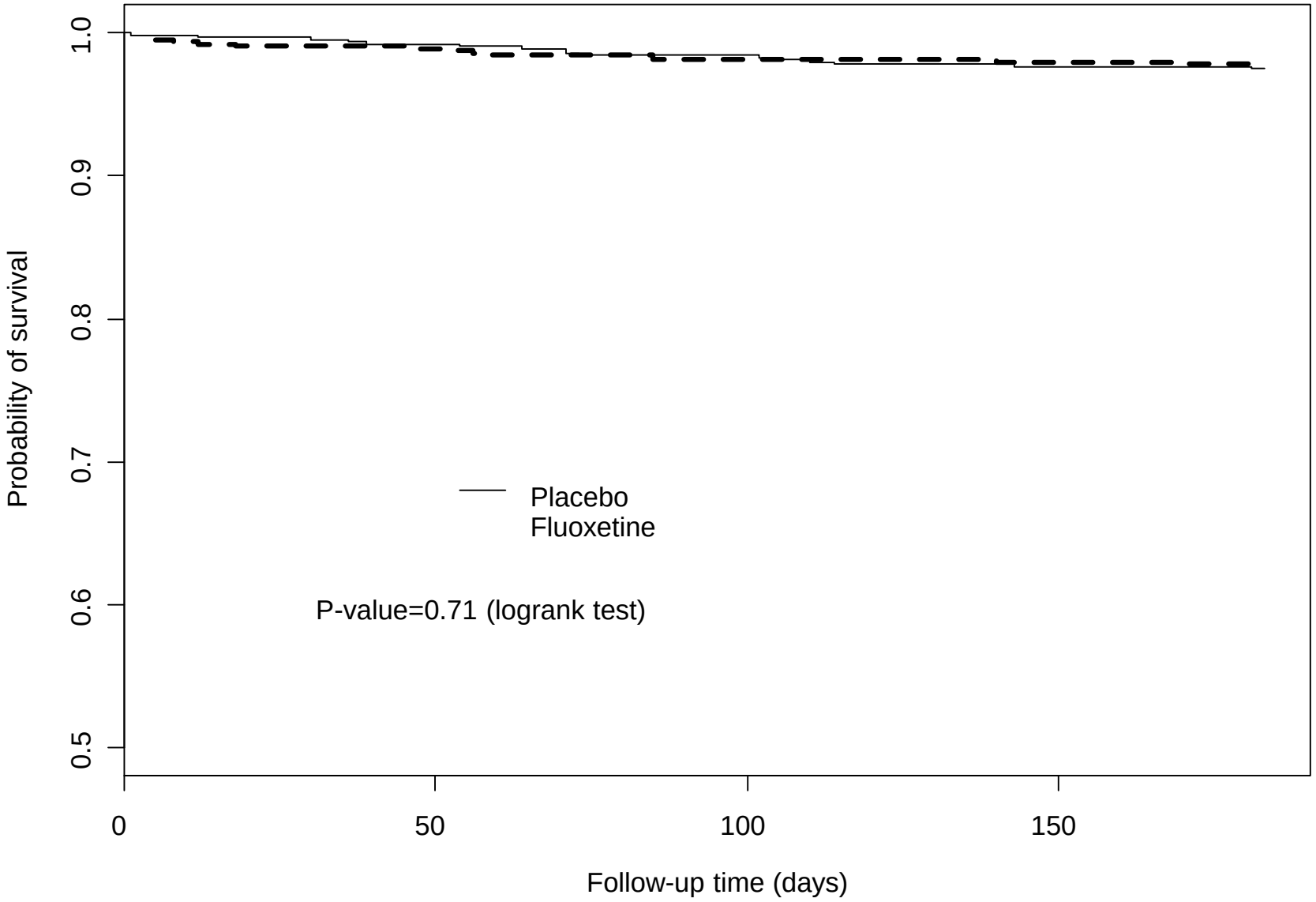


Supplementary figure 1. Kaplan Meier curve of time to permanent discontinuation of trial medication.

Subgroup	Sample size Fluoxetine	placebo	Common OR (95%CI)	P-value for Interaction
Country				
AU/NZ	284	274	0.819 [0.602,1.115]	0.28
VN	340	358	1.052 [0.797,1.39]	
Age				
<=70	440	429	0.947 [0.737,1.217]	0.74
>70	184	203	0.896 [0.624,1.286]	
Time from stroke onset to randomisation				
2-8 day	475	473	0.865 [0.682,1.097]	0.17
9-15days	149	159	1.201 [0.793,1.82]	
Stroke pathology				
Ischaemic	534	537	0.948 [0.758,1.185]	0.98
Haemorrhagic	87	94	0.905 [0.528,1.553]	
Stroke severity				
NIHSS 0-5	291	303	0.899 [0.659,1.228]	0.58
NIHSS >5	333	329	0.998 [0.756,1.317]	
Motor deficit (NIHSS)				
Yes	544	543	1.008 [0.809,1.256]	0.07
No	80	89	0.649 [0.357,1.18]	
Aphasia (NIHSS)				
Yes	124	120	0.747 [0.467,1.196]	0.21
No	500	512	1.000 [0.796,1.258]	
Prob. of being alive and independent at 6 months				
0-<=0.15	96	101	0.820 [0.494,1.361]	0.71
>0.15 to 1	528	531	0.948 [0.756,1.189]	
Depression at baseline				
Yes	14	17	0.654 [0.161,2.666]	0.88
No	610	615	0.939 [0.762,1.156]	
Consent given by				
Patient	334	324	0.857 [0.642,1.143]	0.59
Person resposible or Proxy	280	295	0.980 [0.725,1.325]	
Overall	624	632	0.936 [0.762,1.15]	



Supplementary figure 2. Primary outcome by pre-specified subgroups.



Supplementary figure 3. Kaplan Meier survival curve to 6 months follow-up.